The Year in Cardiology 2013: heart failure

Ertl, G ; Ruschitzka, F

Abstract: Heart failure has become a worldwide epidemic of the 21st century with increasing impact on healthcare systems. The 2012 ESC and 2013 ACCF/AHA guidelines have set the stage for current therapy to reduce mortality and morbidity. There is a dawn of hope for therapy of acute and diastolic heart failure; it has become clearer that patients benefit from mitral reconstruction and which patients benefit from heart failure management programmes; genetics and proteomics advance in great strides; competing concepts of cell therapy seem to spiral, hopefully upwards; and we can further nurture our hope for evidence-based individualized diagnostic and therapy.

DOI: https://doi.org/10.1093/eurheartj/eht555

European Heart Journal (2014) **35**, 470–473
doi:10.1093/eurheartj/eht555

The Year in Cardiology

The Year in Cardiology 2013: heart failure

Georg Ertl[1]* and Frank Ruschitzka[2]

[1]Medizinische Klinik 1/Deutsches Zentrum für Herzinsuffizienz, Würzburg, Germany; and [2]Cardiovascular Center, University Hospital Zurich, Zurich, Switzerland

Received 13 November 2013; revised 27 November 2013; accepted 3 December 2013; online publish-ahead-of-print 2 January 2014

Heart failure has become a worldwide epidemic of the 21st century with increasing impact on healthcare systems. The 2012 ESC and 2013 ACCF/AHA guidelines have set the stage for current therapy to reduce mortality and morbidity. There is a dawn of hope for therapy of acute and diastolic heart failure; it has become clearer that patients benefit from mitral reconstruction and which patients benefit from heart failure management programmes; genetics and proteomics advance in great strides; competing concepts of cell therapy seem to spiral, hopefully upwards; and we can further nurture our hope for evidence-based individualized diagnostic and therapy.

Keywords Heart failure

Introduction

Heart failure has become a worldwide epidemic of the 21st century with increasing impact on healthcare systems. The 2012 ESC and 2013 ACCF/AHA guidelines have set the stage for current therapy to reduce mortality and morbidity.[1,2] The guidelines are valid and based on study evidence for therapy of chronic systolic left heart failure of patients without comorbidities (*Figure 1*). They admit that evidence is sparse for diagnostics, acute heart failure, co-morbidities, heart failure with preserved ejection fraction (HFpEF), many surgical procedures, and end-of-life care. In addition, it can be questioned whether the same therapy fits to any aetiology and genetic background of individual patients. Adding further principles of neurohumoral inhibition did not further improve therapy. Thus, many questions are left by the ESC-guideline 2012 and ACC/AHA guideline 2013 to be answered by research in 2013 and in the future.

Heart failure diagnostics, evidence of no evidence

While conventional echocardiography remains the bread-and-butter technique, the value of speckle tracking has recently been proposed for estimating prognosis and as a clue in differential diagnosis.[3] Magnetic resonance imaging may detect and localize fibrosis and subtle changes of circumferential strain in an asymptomatic population[4] as prognostic indicators of heart failure admission and mortality. Analysis of biomarkers or specific features in imaging may contribute to better understanding of mechanisms and have the potential to individualize prevention and therapy. So far, the consequences remain unclear of such studies for therapy.

Controlled endpoint studies for diagnostics are missing in patients with heart failure. In addition, heart failure therapy requires information on an aetiology and potential complications, in other words, it is compulsory to combine all clinical information, relevant laboratory tests, and imaging for diagnostics. Thus, diagnostic tools need to be evaluated in the context of diagnostic algorithms rather than in protocols insensitive to information obtained by complementary or competing methods. These studies are virtually missing and guidelines remain on the level of expert recommendations.[1,2]

Acute heart failure, a dawn of hope for therapy?

Acutely decompensated heart failure has recently been recognized as an entity which severely burdens prognosis. The challenge combatting acute heart failure has generated a number of trials with classic as well as innovative drugs such as levosimendan, nesiritide, rolofylline, tezosentan, and omecamtivmecarbil: so far in vain. Only recently, a dawn of hope has come up with the peptide relaxin-2, which regulates circulation and renal perfusion in pregnancy. Serelaxin, the recombinant human relaxin-2, reduced a dyspnoea score which was a primary endpoint, and 180-day mortality which was a tertiary endpoint.[5] A clue for the success of this study may have been the exclusion of hypotensive patients. This and other principles are currently

The opinions expressed in this article are not necessarily those of the Editors of the *European Heart Journal* or of the European Society of Cardiology.

* Corresponding author. Email: ertl_g@medizin.uni-wuerzburg.de

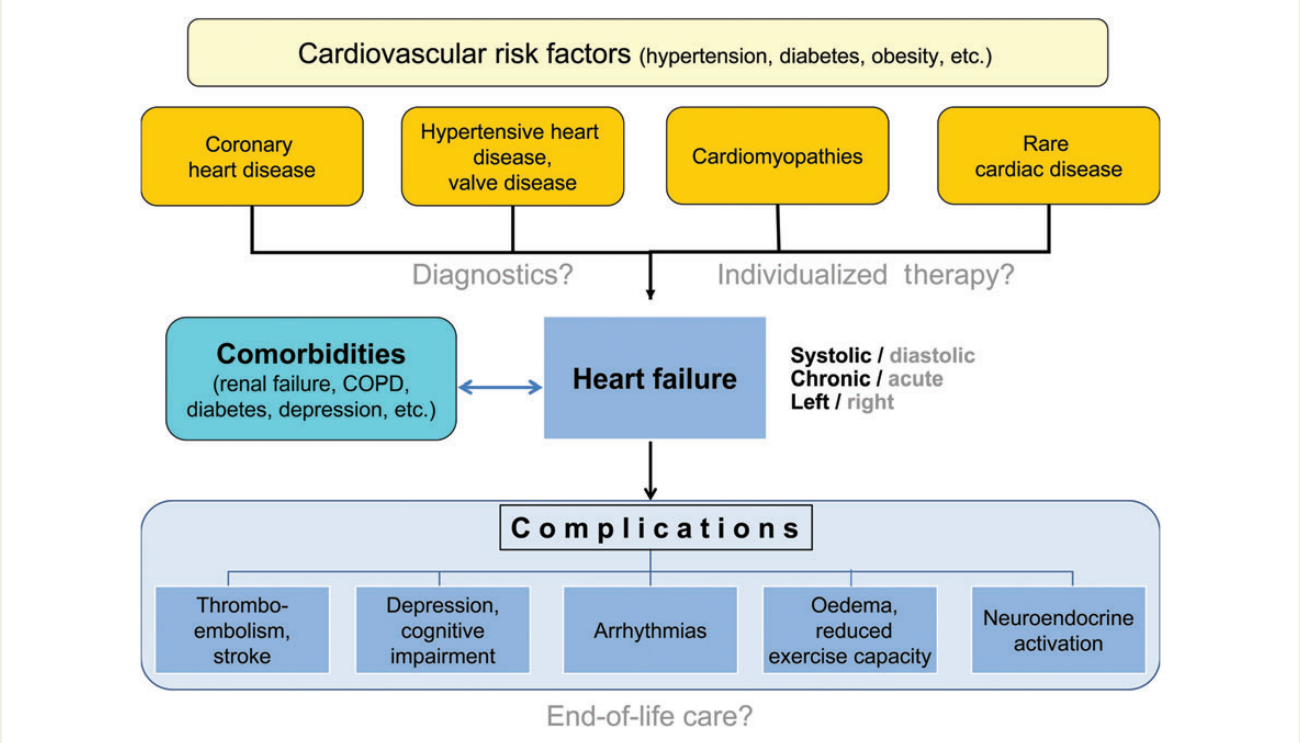

Figure 1 Patients may develop heart failure on the basis of various cardiovascular risk factors and heart diseases. Numerous comorbidities and complications add up to the high complexity of heart failure. Gaps in evidence of the ESC-guideline 2012 include diagnostics, acute heart failure, co-morbidities, diastolic heart failure, many surgical procedures, individualized therapy, and end-of-life care.

being followed up including studies with mortality as a primary endpoint.

Heart failure in real life: managing co-morbidities

'The systemic disease "heart failure" starts before clinical manifestation'.[6] This may be due to the underlying disease which may be systemic like atherosclerosis, to multiple organ complications of heart failure, or the omnipresence of comorbidities. The Meta-analysis Global Group in Chronic Heart Failure has reported on almost 40 000 patients with chronic heart failure. Next to age, male gender, ejection fraction, New York Heart Association class, renal failure, diabetes, and chronic obstructive pulmonary disease were confirmed as comorbid predictors of mortality.[7] The EHJ column 'The heart and other organs' discussed interactions of the heart with the gut, liver, kidney, and the bronchopulmonary system. Cognition deficiency and depression severely burden on morbidity and mortality. The diversity of multimorbidity and consequent polypharmacy is incompatible with the reductive concept of clinical studies and requires a more comprehensive approach. Recent guidelines consider this inconsistency but do not offer solutions. At least they suggest management programmes for selected patients. Results of controlled studies on such programmes have been controversial but after all it seems that nurse-and-doctor-based programmes may be extremely effective in advanced heart failure.[8] Telemetry may supplement these programmes. At least patients with implanted devices seem to have benefits from telemonitoring technology (In Time Study ESC Highlights 2013). Less ill patients get by with the management of their general practitioner.[9]

Heart failure with preserved ejection fraction, a surrogate for comorbidity?

For years, clinical studies on HFpEF have been most frustrating. The concepts for treating heart failure with reduced ejection fraction generally have failed in large HFpEF trials. Prevalence of HFpEF seems to rise in our aging society and patients appear to become more and more multimorbid. Two latest studies may exemplify the problem.[10,11] The aldosterone antagonist spironolactone showed some benefit on left ventricular diastolic function in the Aldo-DHF study but did not reduce the combined cardiovascular primary outcome in the TOPCAT trial (late breaking session at AHA 2013). The RELAX study, testing the effect of the phosphodiesterase-5 inhibitor sildenafil, was completely negative. In the RELAX trial, 43% had diabetes mellitus, 19% COPD, 51% atrial fibrillation or flutter, and 35% anaemia. In the Aldo-DHF study, comorbidities were present but prevalence was somewhat lower (diabetes: 17%, COPD: 3%, a trial fibrillation: 5%, average Hb: 13.8 g/dL). Nevertheless, comorbidities may dominate the course of heart failure and may thus defeat potential benefit of a cardiovascular approach of therapy.

In this clinical syndrome, physical exercise could be an attractive alternative to drugs since it may have beneficial effects on HFpEF as well as on various comorbidities.

Individualized medicine

Daily life medicine needs to individualize heart failure therapy considering specific patient requirements and requests including but also beyond evidence offered by guidelines. There have been strong concepts deriving an individualized approach from pathophysiologic considerations. One example may be cardiac resynchronization therapy (CRT) which has proved to be beneficial for patients even in mild heart failure but with wide bundle branch block and asynchronous left ventricular contraction. Pressure from various sides is high to widen the indication to a more general population who does not meet the criteria which have been the conceptual basis for this therapy. It needed a large trial to show that patients with systolic heart failure and a QRS duration of $<$130 ms had no benefit from CRT.[12] This negative trial was of particular value since it answered a clinically most relevant question but also proved the pathophysiologic concept which confines CRT.

Personalized medicine may substantially add to this approach if it includes all available information. Genome-wide association studies (GWAS) and plasma proteomics may identify potential new biomarkers for hypertrophy, and chronic or acutely decompensated heart failure. Variants of genes involved in free radical generation, dysregulation of iron homeostasis, and accumulation of cardiotoxicanthracyclines may predict anthracycline-induced cardiotoxicity.[13] However, the combination of genetic and clinical information performs superior. This may impact on the indication for early heart failure therapy and/or on a potential future specific preventive therapy perhaps with a small molecule that selectively binds to TOP2B.[14] Genome-wide association studies may identify novel risk loci and genetic predisposition for cardiac disease. Thus, GWAS may put forward hypotheses for mechanisms which may be substantiated by functional studies and then give rise to new therapies. Obviously, genetics may be most valuable in rare and monogenetic disease. But cardiac hypertrophy and failure are regulated on transcriptional, translational, and post-translational levels.[15] The majority of our patients need to rely on our capability to adjust guidelines to their individual condition.

Surgical procedures

Heart failure surgery has become a rapidly evolving field. Mechanical-assist technology develops so fast that most studies finish up with an outdated device. Most spectacular progress has been made in valve surgery. Mitral valve reconstruction is clearly superior to artificial valves. The Mitral Regurgitation International Database has shown in 1021 patients that early mitral reconstruction compared with initial medical therapy reduced mortality and the risk of heart failure.[16] In ischaemic mitral regurgitation, valve repair and replacement revealed similar end-systolic volumes at 12 months but in the repair group recurrence of moderate-to-severe mitral regurgitation was high (32.6% vs. 2.3%, in replacement).[17] Valve surgery has got strong competition by interventional procedures with potential impact on heart failure; this will be discussed elsewhere in this journals issue. In contrast, surgical left ventricular reconstruction still awaits the definition of the subgroup of heart failure patients which may profit from the procedure.[18] Hasty conclusions from the STICH-trial that viability testing is not needed may hamper further in depth research. Results of the STICH-trial may have been different if viability testing had been used in all patients for triage to preselected procedures. Studies are urgently required which predefine meticulously patients by testing for ischaemia and viability. Individualized therapy is probably most important for surgical decisions.

New principles in therapy

Despite success of standard heart failure therapy, morbidity and mortality remain unacceptably high. Adding angiotensin receptor blockers (ARBs) or the renin inhibitor aliskiren to standard angiotensin converting enzyme inhibitors (ACEIs) has not added benefit but increased side effects.[19] These studies suggest that the principle of inhibiting the renin-angiotensin system has reached its limits. It remains unclear whether aliskiren *instead* of an ARB or ACEI would have been superior to the older drugs or that the combination could be effective in certain subgroups like patients without diabetes mellitus. The ethical consideration that standard therapy may not be withheld from our study patients and that new drugs have to be tested *on top* of standard therapy creates a difficult situation for clinical research. Angiotensin converting enzyme inhibitors have been tested against previously available vasodilators, and ARB's against ACEI. We probably have to bring the dogma in question since drugs may be better *instead of*, but not *on top of* standard therapy. This is considered in the ongoing ATMOSPHERE[20] trial which includes an arm testing aliskiren vs. enalapril.

We also have to think about reducing the number of pills and principles considering the polypharmacy faced by our multimorbid heart failure patients. It seems that we are well on the way to lose one principle. Studies have suggested no benefit but rather increased mortality among patients taking digoxin even in the presence of a trial fibrillation. But digitalis has been declared dead many times and further retrospective analyses or registries add only weak evidence to weak evidence. Anyway, there are strong rationales for the need of new concepts in drug therapy rather than for new drugs in established concepts. Of those which have reached the clinical study level, intravenous ferric carboxymaltose may represent such a new concept. The independence of its effects from anaemia suggests indeed new and so far unknown mechanisms of action. Neutral endopeptidase (neprylisin) inhibition or novel soluble guanylatecyclase stimulators like riociguat may be other semi-new concepts. Other new concepts are promising but have not yet made it to clinical testing. Gene therapy may address receptors or receptor-kinase expression so far not approachable by conventional drugs. Therapy with or against microRNA is another principle awaiting clinical evaluation.[21] Finally, there are major efforts ongoing to establish cell therapy. Shock wave-facilitated intracoronary administration of bone marrow cells[22] or endogenous cardiac stem cells[23] may contribute to improved cardiac function.

Conclusions

Numerous questions in heart failure research are left by the year 2013 to be answered by research in 2014. Many evidence blanks in

the actual guidelines have still remained but we have got closer to fill some of them. There is some hope for therapy of acute and diastolic heart failure. Progress in cardiac surgery and valve interventions still await prove of their relevance for the course of heart failure. It has become clearer which patients benefit from heart failure management programmes. Competing concepts of cell therapy seem to spiral, hopefully upwards; genetics and proteomics are still a long way off heart failure management but we can further nurture our hope for evidence-based individualized diagnostics and therapy. All these advances will further add to the complexity of heart failure management, and research will require more and more interdisciplinarity.

Conflict of interest: G.E. received grants from Novartis, Boehringer, Bayer, Pfizer. F.R. received grants from Roche. Consultancy activities for Biotronik and Cardiorentis, speakers bureau Servier and St Jude Medical.

References

1. McMurray JJV, Adamopoulos S, Anker SD, Auricchio A, Böhm M, Dickstein K, Falk V, Filippatos G, Fonseca C, Gomez-Sanchez MA, Jaarsma T, Køber L, Lip GYH, Maggioni AP, Parkhomenko A, Pieske BM, Popescu BA, Rønnevik PK, Rutten FH, Schwitter J, Seferovic P, Stepinska J, Trindade PT, Voors AA, Zannad F, Zeiher A. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012. *Eur Heart J* 2012;**33**:1787–1847.
2. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Drazner MH, Fonarow GC, Geraci SA, Horwich T, Januzzi JL, Johnson M, Kasper EK, Levy WC, Masoudi FA, McBride PE, McMurray JRJV, Mitchell JE, Peterson PN, Riegel B, Sam F, Stevenson LW, Tang WHW, Tsai EJ, Wilkoff BL. 2013 ACCF/AHA Guideline for the Management of Heart Failure: Executive Summary: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation* 2013;**128**:1810–1852.
3. Krämer J, Niemann M, Liu D, Hu K, Machann W, Beer M, Wanner C, Ertl G, Weidemann F. Two-dimensional speckle tracking as a non-invasive tool for identification of myocardial fibrosis in Fabry disease. *Eur Heart J* 2013;**34**:1587–1596.
4. Choi E-Y, Rosen BD, Fernandes VRS, Yan RT, Yoneyama K, Donekal S, Opdahl A, Andre LC, Almeida ALC, Wu CO, Gomes AS, Bluemke DA, Lima JAC. Prognostic value of myocardial circumferential strain for incident heart failure and cardiovascular events in asymptomatic individuals: the Multi-Ethnic Study of Atherosclerosis. *Eur Heart J* 2013;**34**:2354–2361.
5. Teerlink JR, Cotter G, Davison BA, Felker GM, Filippatos G, Greenberg BH, Ponikowski P, Unemori E, Voors AA, Adams Jr KF, Dorobantu MI, Grinfeld LR, Jondeau G, Marmor A, Masip J, Pang PS, Werdan K, Teichman SL, Trapani A, Bush CA, Saini R, Schumacher C, Severin TM, Metra M, for the RELAXin in Acute Heart Failure (RELAX-AHF) Investigators. Serelaxin, recombinant human relaxin-2, for treatment of acute heart failure (RELAX-AHF): a randomised, placebo-controlled trial. *Lancet* 2013;**381**:29–39.
6. Ertl G, Frantz S. Adverse cardiac remodeling: phosphoinositide 3-kinase another unique factor in a multifactorial condition. *Circulation* 2012;**126**:2175–2176.
7. Pocock SJ, Ariti C, McMurray JJV, Maggioni A, Kober L, Squire IB, Swedberg K, Dobson J, Poppe KK, Whalley GA, Doughty RN. Predicting survival in heart failure: a risk score based on 39 372 patients from 30 studies. *Eur Heart J* 2013;**34**:1404–1413.
8. Angermann CA, Stoerk S, Gelbrich G, Faller H, Jahns R, Frantz S, Loeffler M, Ertl G. Mode of action and effects of standardized collaborative disease management on mortality and morbidiy in patients with systolic heart failure: the interdisciplinary network for heart failure (INH) study. *Circ Heart Fail* 2012;**5**:25–35.
9. Schou M, Gustafsson F, Videbaek L, Tuxen C, Keller N, Handberg J, Knudsen AS, Espersen G, Markenvard J, Egstrup K, Ulriksen H, Hildebrandt PR, on behalf of the NorthStar Investigators, all members of The Danish Heart Failure Clinics Network. Extended heart failure clinic follow-up in low-risk patients: a randomized clinical trial (NorthStar). *Eur Heart J* 2013;**34**:432–442.
10. Edelmann F, Wachter R, Schmidt AG, Kraigher-Krainer E, Colantonio C, Kamke W, Duvinage A, Stahrenberg R, Durstewitz K, Löffler M, Düngen H-D, Tschöpe C, Herrmann-Lingen C, Halle M, Hasenfuss G, Gelbrich G, Pieske B, for the Aldo-DHF Investigators. Effect of spironolactone on diastolic function and exercise capacity in patients with heart failure with preserved ejection fraction. The Aldo-DHF Randomized Controlled Trial. *JAMA* 2013;**309**:781–791.
11. Redfield MM, Chen HH, MD Borlaug BA, Semigran MJ, Lee KL, Lewis G, LeWinter MM, Rouleau JL, Bull DA, Mann DL, Deswal A, Stevenson LW, Givertz MM, Ofili EO, O'Connor CM, Patel MR, Kim RJ, Tracy RP, Velazquez EJ, Anstrom KJ, Hernandez AF, Mascette AM, Braunwald E, for the RELAX Trial. Sildenafil and exercise capacity in heart failure. *JAMA* 2013;**310**:432–433.
12. Ruschitzka F, Abraham WT, Singh JP, Bax JJ, Borer JS, Brugada J, Dickstein K, Ford I, Gorcsan J III, Gras D, Krum H, Sogaard P, Holzmeister J, for the EchoCRT Study Groupet *al.* Cardiac-resynchronization therapy in heart failure with a narrow QRS complex. *N Engl J Med* 2013;**369**:1395–1405.
13. Armenian SH, Ding Y, Mills G, Sun C, Venkataraman K, Wong FL, Neuhausen SL, Senitzer D, Wang S, Forman SJ, Bhatia S. Genetic susceptibility to anthracycline-related congestive heart failure in survivors of haematopoietic cell transplantation. *British J Haematol* 2013;**163**:205–213.
14. Zhang S, Liu X, Bawa-Khalfe T, Lu LS, Lyu YL, Liu LF, Yeh ET. Identification of the molecular basis of doxorubicin-induced cardiotoxicity. *Nat Med* 2012;**18**:1639–1642.
15. Anand P, Brown JD, Lin CY, Qi J, Zhang R, Artero PC, Alaiti MA, Bullard J, Alazem K, Margulies KB, Cappola TP, Lemieux M, Plutzky J, Bradner JE, Haldar SM. Bromodomains mediate transcriptional pause release in heart failure. *Cell* 2013;**154**:569–582.
16. Suri RM, Vanoverschelde J-L, Grigioni F, Schaff HV, Tribouilloy C, Avierinos J-F, Barbieri A, Pasquet A, Huebner M, Rusinaru D, Russo A, Michelena HI, Enriquez-Sarano M. Association between early surgical intervention vs watchful waiting and outcomes for mitral regurgitation due to flail mitral valve leaflets. *JAMA* 2013;**310**:609–616.
17. Acker MA, Parides MK, Perrault LP, Moskowitz AJ, Gelijns AC, Voisine P, Smith PK, Hung JW, Blackstone EH, Puskas JD, Argenziano M, Gammie JS, Mack M, Ascheim DD, Bagiella E, Moquete EG, Ferguson TB, Horvath KA, Geller NL, Miller MA, Woo JY, D'Alessandro DA, Ailawadi G, Dagenais F, Gardner TJ, O'Gara PT, Michler RE, Kron IL, for the CTSN. Mitral-valve repair versus replacement for severe ischemic mitral regurgitation. *N Engl J Med*. Published online ahead of print 18 November 2013.
18. Oh JK, Velazquez EJ, Menicanti L, Pohost GM, Bonow RO, Lin G, Hellkamp AS, Ferrazzi P, Wos S, Rao V, Berman D, Bochenek A, Cherniavsky A, Rogowski J, Rouleau JL, Lee KL, on behalf of the STICH Investigators. Influence of baseline left ventricular function on the clinical outcome of surgical ventricular reconstruction in patients with ischaemic cardiomyopathy. *Eur Heart J* 2013;**34**:39–47.
19. Gheorghiade M, Böhm M, Greene SJ, Fonarow GC, Lewis EF, Zannad F, Solomon SD, Baschiera F, Botha J, Hua TA, Gimpelewicz CR, Jaumont X, Lesogor A, Maggioni AP, for the ASTRONAUT Investigators and Coordinators. Effect of Aliskiren on post-discharge mortality and heart failure readmissions among patients hospitalized for heart failure. *JAMA* 2013;**309**:1125–1135.
20. Krum H, Massie B, Abraham WT, Dickstein K, Kober L, McMurray JJ, Desai A, Gimpelewicz C, Kandra A, Reimund B, Rattunde H, Armbrecht J. ATMOSPHERE Investigators. Direct renin inhibition in addition to or as an alternative to angiotensin converting enzyme inhibition in patients with chronic systolic heart failure: rationale and design of the Aliskiren Trial to Minimize OutcomeS in Patients with HEart failuRE (ATMOSPHERE) study. *Eur J Heart Fail* 2011;**13**:107–114.
21. Boon RA, Iekushi K, Lechner S, Seeger T, Fischer A, Heydt S, Kaluza D, Tréguer K, Carmona G, Bonauer A, Horrevoets AJ, Didier N, Girmatsion Z, Biliczki P, Ehrlich JR, Katus HA, Müller OJ, Potente M, Zeiher AM, Hermeking H, Dimmeler S. MicroRNA-34a regulates cardiac ageing and function. *Nature* 2013;**495**:107–110.
22. Assmus B, Walter DH, Seeger FH, Leistner DM, Steiner J, Ziegler I, Lutz A, Khaled W, Klotsche J, Tonn T, Dimmeler S, Zeiher AM. Effect of shock wave-facilitated intracoronary cell therapy on LVEF in patients with chronic heart failure. *JAMA* 2013;**309**:1622–1631.
23. Ellison GM, Vicinanza C, Smith AJ, Aquila I, Leone A, Waring CD, Henning BJ, Stirparo GG, Papait R, Scarfo M, Agosti V, Viglietto G, Condorelli G, Indolfi C, Ottolenghi S, Torella D, Nadal-Ginard B. Adult c-kitpos cardiac stem cells are necessary and sufficient for functional cardiac regeneration and repair. *Cell* 2013;**154**:827–842.